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*OFFICIAL***FACSIMILE COVER PAGE**

TO: Examiner Stephanie Zitomer
COMPANY: PTO - GROUP 1634
FACSIMILE #: 703/308-8724
FROM: Margaret M. Wall
DATE: March 1, 1999

Number of pages, including cover page ~~40~~ 25 Faxed _____

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Message:

DOCKET NO. NEX61/CIP

#12
B. Wehle
3/10/99

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: JANJIC ET AL.)
SERIAL NO: 08/897,351) EXAMINER: ZITOMER, S.
FILED: JULY 21, 1997) ART UNIT: 1634
TITLE: VASCULAR ENDOTHELIAL)
GROWTH FACTOR (VEGF))
NUCLEIC ACID LIGAND)
COMPLEXES)

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

PETITION FOR EXTENSION OF TIME

An Office Action was mailed in the above-captioned patent application on June 8, 1998. Applicant hereby petitions for a three month extension of time, up to December 8, 1998, in which to respond to such Office Action. The undersigned hereby authorizes the fee of \$870.00, and any deficiency, to be charged to Deposit Account No. 22-0277. A copy of this Petition is enclosed for deposit account purposes.

Respectfully submitted,

Date: December 7, 1998

Barry J. Swanson
Barry J. Swanson, # 33,215
Swanson & Bratschun, L.L.C.
8400 E. Prentice Avenue, #200
Englewood, CO 80111
Telephone: (303) 793-3333

37 CFR 1.5

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Assistant Commissioner of Patents, Washington, D.C. 20231 on Dec 7, 1998.

Signature: Tracy E. CrispinName: Tracy E. Crispin

nexagen\ex72\extend.101

B. Webb
3/10/99

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: JANJIC ET AL.)
SERIAL NO: 08/897,351) EXAMINER: ZITOMER, S.
FILED: JULY 21, 1997) ART UNIT: 1634
TITLE: VASCULAR)
ENDOTHELIAL GROWTH)
FACTOR (VEGF))
NUCLEIC ACID LIGAND)
COMPLEXES)

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

AMENDMENT AND REMARKS

An Office Action was issued in the above-referenced application on June 8, 1998. Both pending claims were rejected. This Amendment and Remarks is hereby submitted to respond to such Office Action. Accompanying this response is a Petition for Extension of Time for three months, extending the response date to December 8, 1998. Claims 1-2 are pending and are rejected. Claim 2 has been amended, and claims 3-21 have been added herein. The Applicants respectfully request that the following amendments be entered and remarks be considered.

AMENDMENT

In the Specification

At page 1, line 6, delete "08/____" and insert --08/870,930--.

37 CFR 1.3

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on Dec 8, 1998

Signature: [Signature]Name: T. E. Cristino

At page 1, line 7, delete ", under Express Mail Label No. EM432185810US".

At page 20, line 23, after "SEQ ID NOS:" insert --10-86--.

At page 21, line 7, after "SEQ ID NOS:" insert --10-86--.

At page 40, line 26, delete "SEQ ID NO:1" and insert --SEQ ID NOS:1 and 2--.

At page 40, line 30, delete "ID NO:2" and insert --ID NO:3--.

At page 41, line 1, delete "ID NO:3" and insert --ID NO:4--.

At page 58, line 9, after "SEQ ID NOS:" insert --8 and 9--.

At page 58, line 11, after "SEQ ID NOS:" insert --5-7--.

At page 58, line 19, after "SEQ ID NO:" insert --87--.

At page 58, line 21, after "SEQ ID NO:" insert --88--.

At page 58, line 27, after "SEQ ID NOS:" insert --8 and 9--.

At page 59, line 6, delete "(SEQ ID NOS:)".

At page 62, line 11, after "SEQ ID NO:" insert --8--.

Please delete Tables 1-4 in their entirety and replace them with the enclosed Tables

1-4.

In the Figures

Please replace Figures 1A-1E with the enclosed Figures 1A-1E.

In the Claims

Please amend claim 2 as follows:

2. (amended) A method for [prolonging the residence time] increasing the pharmacokinetic properties of a ^{VEGF}Nucleic Acid Ligand in an [ocular application] ~~[eye]~~ comprising [attaching] covalently linking a Non-Immunogenic, High Molecular Weight compound to a ^{VEGF}Nucleic Acid Ligand to form a complex comprised of a ^{VEGF}Nucleic Acid Ligand and a Non-Immunogenic, High Molecular Weight Compound, and administering said complex [directly] to the eye

Please add the following new claims 3-21.

3. The RNA ligand to VEGF of claim 1 wherein said ligand is selected from the group consisting of the sequences set forth in Tables 1-4 (SEQ ID NOS: 10-86).

4. The RNA ligand of claim 3 wherein said ligand is substantially homologous to and has substantially the same ability to bind VEGF as a ligand selected from the group consisting of the sequences set forth in Tables 1-4 (SEQ ID NOS: 10-86).

5. The RNA ligand of claim 3 wherein said ligand has substantially the same structure and substantially the same ability to bind VEGF as a ligand selected from the group consisting of the sequences set forth in Tables 1-4 (SEQ ID NOS: 10-86).

B2
cont
6. The RNA ligand to VEGF of claim 1 identified according to the method comprising:

a) contacting a Candidate Mixture of RNA with VEGF, wherein the RNA having an increased affinity to VEGF relative to the Candidate Mixture may be partitioned from the remainder of the Candidate Mixture;

b) partitioning the increased affinity RNA from the remainder of the Candidate Mixture; and

c) amplifying the increased affinity RNA to yield a mixture of RNA enriched for RNA having an increased affinity for VEGF; whereby RNA Ligands of VEGF are identified.

7. The RNA ligand to VEGF of claim 3 identified according to the method comprising:

a) contacting a Candidate Mixture of RNA with VEGF, wherein the RNA having an increased affinity to VEGF relative to the Candidate Mixture may be partitioned from the remainder of the Candidate Mixture;

b) partitioning the increased affinity RNA from the remainder of the Candidate Mixture; and

c) amplifying the increased affinity RNA to yield a mixture of RNA enriched for RNA having an increased affinity for VEGF; whereby RNA Ligands of VEGF are identified.

8. A Complex comprised of the RNA ligand to VEGF of claim 1 and a Non-Immunogenic, High Molecular Weight Compound.

9. The Complex of Claim 8 further comprising a Linker between said ligand and said Non-Immunogenic, High Molecular Weight Compound.

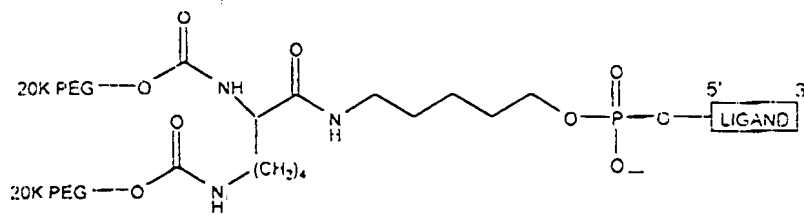
10. The Complex of Claim 8 wherein said Non-Immunogenic, High Molecular Weight Compound is a Polyalkylene Glycol.

11. The Complex of claim 10 wherein said Polyalkylene Glycol is polyethylene glycol.

12. The Complex of claim 11 wherein said polyethylene glycol has a molecular weight of about ~~between~~ 10-80 Kd.

13. The Complex of claim 11 wherein said polyethylene glycol has a molecular weight of about ~~between~~ 20-45 Kd.

14. The Complex of claim 11 wherein said Complex is

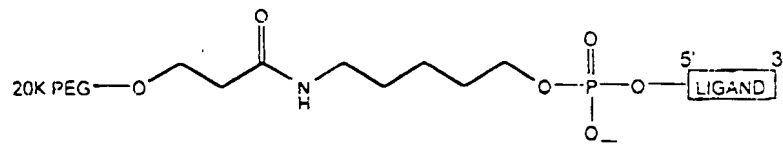


Ligand Component =

fCmGmGrArAfUfCmAmGfUmGmAmAfUmGfCfUfUmAfUmAfCmAfUfCfCmG-3'3'-dT (SEQ ID NO: 8).

(VEGF ligand)

15. The Complex of claim 11 wherein said Complex is



Ligand Component =

fCmGmGrArAfUfCmAmGfUmGmAmAfUmGfCfUfUmAfUmAfCmAfUfCfCmG-3'3'-dT
(VEGF ligand) (SEQ ID NO: 9).

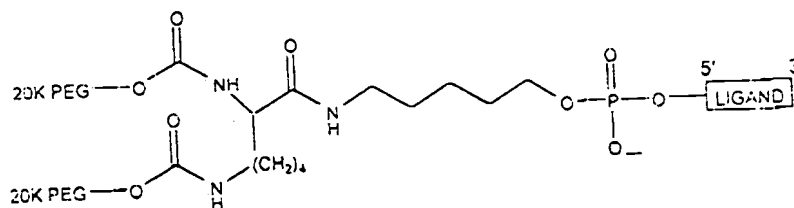
16. The method of claim 2 wherein said Non-Immunogenic, High Molecular Weight Compound is a Polyalkylene Glycol.

17. The method of claim 16 wherein said Polyalkylene Glycol is polyethylene glycol.

18. The method of claim 17 wherein said polyethylene glycol has a molecular weight of about ~~between~~ 10-80 Kd.

19. The method of claim 17 wherein said polyethylene glycol has a molecular weight of about 20-45 Kd.

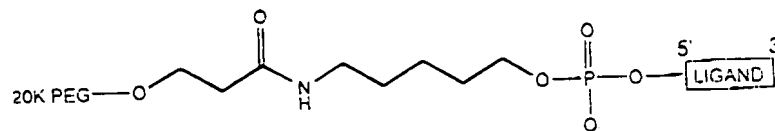
20. The method of claim 19 wherein said complex has the structure



Ligand Component =

fCmGmGrArAfUfCmAmGfUmGmAmAfUmGfCfUfUmAfUmAfCmAfUfCfCmG-3'3'-dT
~~(VEGF ligand)~~ (SEQ ID NO:8).

21. The complex of claim 19 wherein said complex is



Ligand Component =

fCmGmGrArAfUfCmAmGfUmGmAmAfUmGfCfUfUmAfUmAfCmAfUfCfCmG-3'3'-dT
~~(VEGF ligand)~~ (SEQ ID NO:9).

REMARKS

An Office Action was issued in the above-referenced application on June 8, 1998. All examined claims were rejected. This Amendment and Remarks has been made to respond to such Office Action. Claim 2 is amended and claims 3-21 are added herein. Additional amendments have been made by the Applicants without suggestion by the Examiner, but with the same goal in mind. Any amendments that are made that limit the scope of the claims in any way are done so without prejudice. Claims 3-21 are dependent on either claim 1 or claim 2 and relate to embodiments that are clearly supported in the specification.

Notice to Comply with Sequence Rules

Applicants submitted a response to the Notice to Comply with Requirements for Patent Applications containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures on July 7, 1998.

Informalities

The Examiner has objected to the disclosure because nucleotide sequences in the specification, tables and figures lack SEQ ID NOS. Applicants have added the appropriate SEQ ID NOS to Tables 1-4 and Figures 1A-1E and are submitting substitute tables and figures with this document. Furthermore, the specification has been amended to include SEQ ID NOS where appropriate. Applicants assert that the amendments and the substitute tables and figures do not add any new matter to the application or affect the claimed invention. Withdrawal of this objection is respectfully requested.

Rejections under 35 U.S.C. §112, second paragraph

Claim 2 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim has been amended to specifically address points (a), (b), and (d).

With respect to point (c), the Examiner states that the claim is indefinite in reciting "nucleic acid ligand" which is a general term lacking definition or specificity. Applicants respectfully disagree. Applicants wish to direct the Examiner's attention to page 17, lines 4-26 of the specification where Nucleic Acid Ligand is specifically defined. There is no apparent ambiguity with respect to the definition of this term. As this term has been clearly defined in the specification, withdrawal of this rejection is respectfully requested.

Double Patenting Rejection - Obviousness Type

Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 and 11-13 of United States Patent Application No. 08/447,169 (now United States Patent No. 5,811,533) in view of Toole et al. (WO 92/14843). In an effort to expedite prosecution.

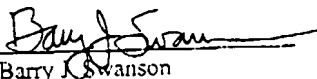
Applicants are submitting herewith a Terminal Disclaimer that disclaims the term of the patent issuing on the subject application beyond the term of the aforementioned patent. NeXstar Pharmaceuticals, Inc., is the assignee of record of the entire interest in United States Patent No. 5,811,533. Thus, NeXstar Pharmaceuticals, Inc. is the owner of the subject application and the patent cited by the Examiner. In view of this submission, it is respectfully requested that the provisional obviousness-type double patenting rejection be withdrawn.

Applicants assert that the above-captioned application is in condition for allowance. Prompt consideration of this Amendment and Remarks is earnestly solicited.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to Deposit Account No. 22-0277, if not otherwise specifically requested. In addition, the undersigned hereby authorizes the charge of any fee created by the filing of this document to Deposit Account No. 22-0277.

Respectfully submitted,

Date: December 7, 1998


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nexstar\nex61c\p\amendment.351\tec wrd

Table 1. 2'-F-pyrimidine ligands to VEGF165

Ligand (frequency)	5'-gggggacgaugcgg [variable region] cagacgacugcccgca-3'	Sequence of variable region	K _d (nM)	SEQ. ID NO: 10 & 11
Family 1				
VP30.7	B	GAAGAAUUGG UCAUCGUCGUCUCGCGCCUCC	3000	12
VP30.12	AAUACG	GAAGAAUUGG AUACAUAUCUCUGU	7	13
VP30.13 (7)	GAUAACA	GAAGAAUUGG UGAACAACGUGGU	10	14
VP30.16	AUGAUCGCGUAG	GAAGAAUUGG AAGGCCU	6	15
VP30.19	CACUUA	GAAGAAUUGA AUUCCCGCUGGU	9	16
VP30.22 (6)	UAG	GAAGAAUUGG AAGCGAUUUCCUGY	20	17
VP30.25	CGGGAUUUUG	GAAGAAUUGG AUUUGGCCU	20	18
VP30.26 (2)	CGGYACUUUG	GAAGAAUUGA AUUCCCGCU	10	19
VP30.27	B	GAAGAAUUGG AUUAUCGUUACCCCCACCU	400	20
VP30.40	AAACG	GAAGAAUUGG AUACGCAAGCAGUU	6	21
VP30.41	UAG	GAAGAAUUGG AAGCGCUCGULUCCG	7	22
VP30.51 (2)	AGUUUUG	GAAGAAUUGG AUGUCCGAGU	90	23
VP30.54	AAGAAACG	GAAGAAUUGG AGACACGCU	10	24
VP40.4 (5)	B	GAAGAAUUGA UGUUUAUUUGCCUCCGUAUUUCCUGCCG	200	25
VP40.43	ACA	GAAGAAUUGG GCUUGGCAUAUCCUUCUCAGCCG	30	26
VP40.53	UGAGAGAAACG	GAAGAAUUGG AUACGAUACUACUCCGCU	8	27
VT30.4	CUAAGUUUUUG	GAAGAAUUGA AUACUGGU	20	28
VT30.7	UAACCAUG	GAAGAAUUGG CUGCUAUCCU	10	29
VT30.10	AACG	GAAGAAUUGG AUACGUAGCAUGGU	2	30
VT30.13	CAGGAUUUUG	GAAGAAUUGG AUAUUGCCCGa	10	31
VT30.20	AAACG	GAAGAAUUGG AUACCGCUACUUGU	4	32
VT30.52	B	GAAGAAUUGA GCAUCCUUCUCCUGUGCCU	9000	33
VT30.53	AGCUAACG	GAAGAAUUGG AAACAACCCGCU	10	34

K_d SEQ. ID NO:
(pM) 10 & 11

Sequence of variable region

5'-ggaggaggauggg [variable region] cagaggaugccgga-3'

Ligand
(frequency)

Family 2

VP30.2 (5)	gpyga	accca	uggaa	uuu	uggagccg	uccccg	10	35
VP30.5 (4)	gdyca	accca	uugac	guu	uggagccg	ugggla	8	36
VP30.31 (5)	gggga	accca	uugaa	cuu	uggagccg	uagccg	6	37
VP30.43	ggua	accca	uugaa	guu	uggagccg	uagccg	5	38
VP40.9	ggagcaga	accca	uagaa	gaa	uggagccg	ucagcuccg	30	39
VP40.14	guaccagaaugagca	accca	augaa	gaa	cugagccg	uggla	8	40
VP40.17	gggggga	accca	uggaa	ucg	uggagccg	ucagcuccg	10	41
VP30.9 (6)	gggga	accca	uugaa	uuu	uggagccg	uggccg	30	42

62

Family 3

VT30.1 (2)	gggggggg	a	acua	gugaaugcuu	aua	cga	ccguguggla	10	43
VT30.2	gggg		auca	gugaaugcuu	aua	ga	ccgucuccg	2	44
VT30.3 (8)	gggggg	aga	auca	gugaaugcuu	aua	aauc	uccgugla	5	45
VT30.11	gggggg	a	auca	gugaaugcuu	aua	gcuc	cccgugccg	4	46
VT30.15	gggg	a	acca	gugaaugcuu	aua	aga	cugcuccg	3	47
VT30.21	gggggg		auca	gugaaugcuu	aua	ga	ccgaaugccg	6	48
VT30.28	gggggg	aga	auca	gugaaugcuu	aua	aacc	uccgugla	60	49
VT30.29	ggggga		auca	gugaaugcuu	aua	gc	uccgggugcu	10	50
VT30.35	ggg		acca	gugaaugcuu	aua	agccca	uccagccg	N.D.	51
VT30.41	gggggg		cagg	gugaaugcca	aug	uagcuu	uccgugla	40	52
VT30.44	ggggga		auca	gugaaugcuu	aua	ca	uccggcuccg	10	53
VT30.54	ggggg		acua	gugaaugcca	aua	uccuuc	uccg	30	54

Table 2. Effect of truncation on high affinity binding of VEGF ligands.

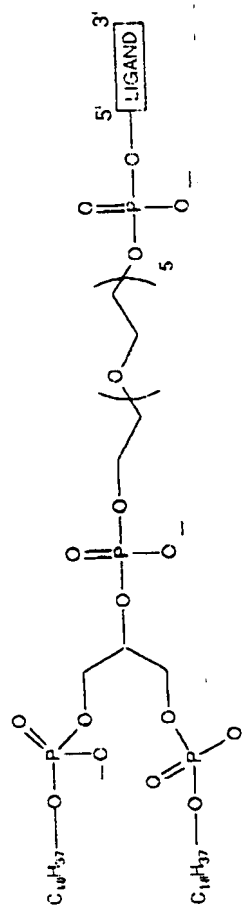
Ligand	Sequence	Length (nts)	K _D (pM)	SEQ ID NO:
t22	GACGAUGCGGUAGGAAGAAUUGGAAGCGC*	29	70	55
t22a	GACGAUGCGGUAGGAAGAAUUGGAAGCG	28	3000	56
t22b	ACGAUGCGGUAGGAAGAAUUGGAAGCGC	28	80	57
t22c	GCGGUAGGAAGAAUUGGAAGCGC	23	90	58
t22d	CGGUAGGAAGAAUUGGAAGCGC	22	100	59
t22e	GGUAGGAAGAAUUGGAAGCGC*	21	200	60
t22f	GUAGGAAGAAUUGGAAGCGC*	20	>100,000	61
t2	GGCGAACCGAUGGAAUUUUUGGACGCUCGCC*	31	20	62
t2a	GCGAACCGAUGGAAUUUUUGGACGCUCGC	29	40	63
t2b	CGAACCGAUGGAAUUUUUGGACGCUCG	27	100	64
t2c	GAACCGAUGGAAUUUUUGGACGCUC*	25	200	65
t2d	AACCGAUGGAAUUUUUGGACGCU*	23	20,000	66
t2e	ACCGAUGGAAUUUUUGGACGC*	21	>100,000	67
t44	GCGGAAUCAGUGAAUGCUUAUACAUCGCG*	29	10	68
t44a	CGGAAUCAGUGAAUGCUUAUACAUCG	27	10	69
t44b	GGAAUCAGUGAAUGCUUAUACAUC	25	60	70
t44c	GAAUCAGUGAAUGCUUAUACAUC*	23	2000	71
t44d	AAUCAGUGAAUGCUUAUACAUC*	21	>100,000	72
t44e	AUCAGUGAAUGCUUAUACA*	19	>100,000	73

Table 3. Effect of 2'-OMe-purine substitutions on affinity for VEGF.

Ligand	Sequence	K _d (pM)	SEQ NO:
t22OMe (OH-10,12,22)	GACGAUGCGGU <u>A</u> GGAAGAAUUGGAAGCGC	10	74
t22OMe (OH-10,12)	GACGAUGCGGU <u>A</u> GGAAGAAUUGGAAGCGC	20	75
t22OMe (OH-10,22)	GACGAUGCGGU <u>A</u> GGAAGAAUUGGAAGCGC	4,000	76
t22OMe (OH-12,22)	GACGAUGCGGU <u>A</u> GGAAGAAUUGGAAGCGC	90	77
t2OMe (OH-6,21)	GGCGA <u>A</u> CCGAUGGAAUUUUUUGGACGCUCGCC	60	78
t2OMe (OH-6)	GGCGA <u>A</u> CCGAUGGAAUUUUUGGACGCUCGCC	500	79
t2OMe (OH-21)	GGCGA <u>A</u> CCGAUGGAAUUUUUGGACGCUCGCC	20,000	80
t44OMe (OH-5,6)	GCGGA <u>A</u> UCAGUGAAUGCUUAUACAUCGCG	40	81
t44OMe (OH-5)	GCGGA <u>A</u> UCAGUGAAUGCUUAUACAUCGCG	>100,000	82
t44OMe (OH-6)	GCGGA <u>A</u> UCAGUGAAUGCUUAUACAUCGCG	>100,000	83

Table 4. Binding Parameters of 2'-Ome-substituted minimal ligands.

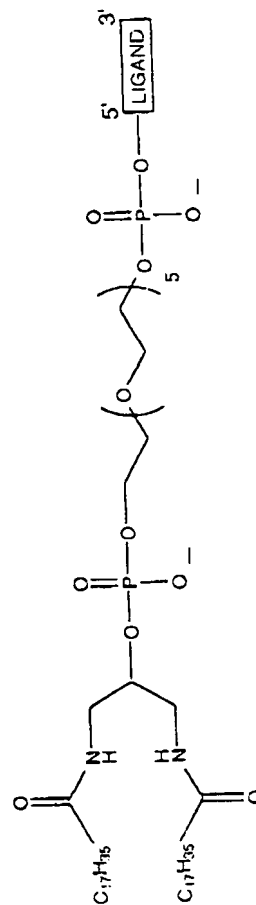
Ligand	Sequence	K_D (s.d.) (pM)	k_d (s.d.) (sec ⁻¹)	k_a (M ⁻¹ sec ⁻¹)	SEQ ID NO:
¹²² OMe	GCGGUAGGAAGAAUUGGAAGCGC	67 (36)	0.012 (0.004)	1.8×10^8	84
¹²⁰ Me	GCGAACCGAUGGAUUUUUGGACGUCGC	140 (50)	0.0042 (0.002)	3.0×10^7	85
¹⁴⁰ Me	CGGAUACAGUGAUGCUUAUACAUCG	51 (11)	0.0074 (0.002)	1.5×10^8	86



NX31838 - PL

Ligand Component =
fCmGmGrArAUICmAmGIUmGmAmAUmGfCIUUmAUmAUICmG-3'3'-dT
(VEGF ligand)

FIGURE 1A SEQ. ID NO.: 5

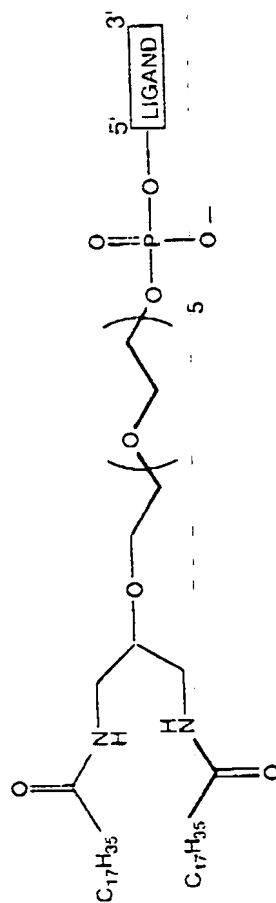


NX31838 Lipid-amide 1

Ligand Component =
fCmGmGrArAUICmAmGIUmGmAmAUmGfCIUUmAUmAUICmG-3'3'-dT
(VEGF ligand)

FIGURE 1B SEQ. ID NO.: 6

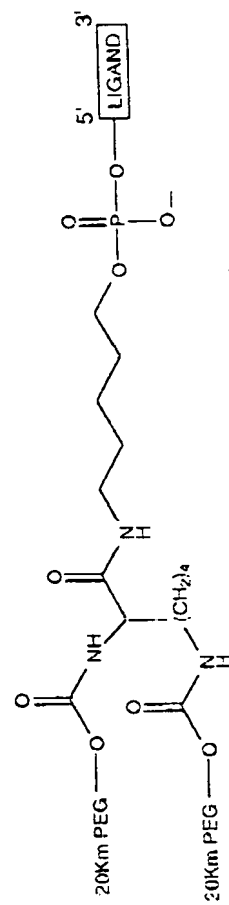
Approved
3-25-99



NX31838 Lipid-amide 2

Ligand Component =
 $fCmGmGrArAUICmAmGfUmGmAmAUmGfCfUfUmAUmAUICmAUICmG-3'3'-dT$
 (VEGF ligand)

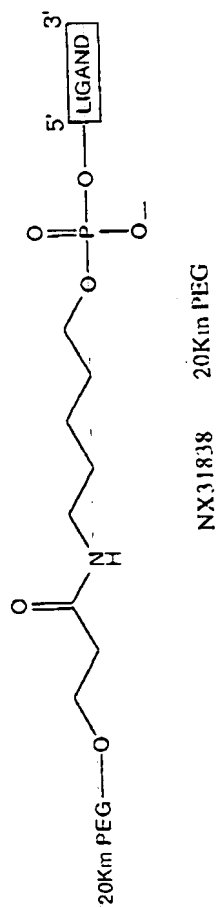
FIGURE 1C SEQ. ID NO.: 7



NX31838 40K mPEG

Ligand Component =
 $fCmGmGrArAUICmAmGfUmGmAmAUmGfCfUfUmAUmAUICmAUICmG-3'3'-dT$
 (VEGF ligand)

FIGURE 1D SEQ. ID NO.: 8



Ligand Component =
fCmGmGrArA/UICmAmG/UmGmAmAfUmGfC/UUmA/UmAICmAUICmG-3'3'-dT
(VEGF ligand)

FIGURE 1E SEQ. ID NO.: 9

In re Application of: JANJIC ET AL.
 Serial No.: 08/897,351
 Filed: JULY 21, 1997
 For: VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) NUCLEIC ACID LIGAND COMPLEXES

ASSISTANT COMMISSIONER FOR PATENTS
 Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.
 In the event that a petition under 37 CFR Section 1.136 is required, but not separated submitted, applicant(s) hereby petition(s) for such an extension of time.
 Small entity status of this application under 37 CFR 1.9 and 1.27 has been established by a verified statement previously submitted.
 A verified statement to establish small entity status under 37 CFR 1.9 and 1.27 is enclosed.
 No additional fee is required.

The fee has been calculated as shown below.

	CLAIMS REMAINING AFTER AMDT.		HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (SMALL ENTITY)	ADD'L FEE (SMALL ENTITY)	RATE	ADD'L FEE
TOTAL	21	MINUS	20	1	x \$9 =	\$	x \$18 =	\$18
INDEP.	2	MINUS	3	0	x \$36 =	\$	x \$	\$0
[First Presentation of Multiple Dep. Claim]					+ \$130 =	\$	+ \$260	\$0
					TOTAL ADD'L FEE	\$	TOTAL ADD'L FEE	\$18

- * If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.
 - ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
 - *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.
- The "Highest Number Previously Paid For" (Total or Independent) is the highest number found from the equivalent box in Col. 1 of a prior amendment or the number of claims originally filed.

It is believed no fees are due. If this is incorrect, please charge by Deposit Account No. 22-0277 for any fees.

Please authorize the \$18.00 additional claim fee to Deposit Account No. 22-0277 (Nexstar Pharmaceuticals, Inc.)

The Commissioner is hereby authorized to charge any underpayment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 22-0277.
 Any filing under 37 CFR 1.16 for the presentation of extra claims.
 Any patent application processing fee under 37 CFR 1.17.

Respectfully submitted,

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37 CFR 1.8

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on

Dec 7-1998

Signature: *Tracy E. Crispino*

Name: Tracy E. Crispino

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Docket #CIP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: JANJIC *ET AL.*)
SERIAL NO: 08/897,351) EXAMINER: ZITOMER, S.
FILED: JULY 21, 1997) ART UNIT: 1807
TITLE: VASCULAR)
ENDOTHELIAL GROWTH)
FACTOR (VEGF))
NUCLEIC ACID LIGAND)
COMPLEXES)

14

TERMINAL DISCLAIMER UNDER 37 CFR §1.321(c)

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

NeXstar Pharmaceuticals, Inc., having a business address of 2860 Wilderness Place, Suite 200, Boulder, CO 80301, is the owner of the entire interest in the instant application, and hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §§ 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior United States Patent No. 5,811,533, issued September 22, 1998. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and United States Patent No. 5,811,533, issued September 22, 1998, are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend beyond the expiration date of the full

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Signature: Tacy E. Crispino

Name: Tacy E. Crispino

Adjustment date: 10/02/2000 PWILSON
03/11/1999 BDEHNY 00000001 220277 08897351
01 FC:148 110.00 CR
02 FC:117 870.00 CR

03/11/1999 BDEHNY 00000001 220277 08897351

01 FC:148 110.00 CH
02 FC:117 870.00 CH

statutory term as defined in 35 U.S.C. §§ 154 to 156 and 173 of United States Patent No. 5,811,533, as presently shortened by any terminal disclaimer, in the event that the foregoing United States Patent: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR §1.321, has all claims canceled by re-examination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

The undersigned is an attorney of record.

The undersigned hereby authorizes the charge of the terminal disclaimer fee of \$110.00 or any deficiency of fees to be charged to Deposit Account No. 22-0277.

Respectfully submitted,

Date: December 7, 1998

Barry J. Swanson

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